2. SYNOPSIS

Study Title:
A Phase 1 Drug-drug Interaction Study of S-217622 With Combined Oral Contraceptives in Healthy Adult Female Participants

Study Number:
2403T1219

Compound:
S-217622 (ensitrelvir)

Trade Name: Not applicable

Sponsor: Shionogi Inc.

Investigators and Study Sites: This study was conducted at 1 site in the US.

Publication (reference): Not applicable

Studied Period: From 11 Sep 2024 (First participant informed consent obtained) to 7 Apr 2025 (Last participant last observation)

Phase of Development: Phase 1

Objectives, Endpoints

Objectives	Endpoints
Primary	
● To investigate the effect of multiple doses of ensitrelvir on the PK of the COC in healthy adult female participants.	● The following PK parameters for EE and DRSP were calculated: C_{max}, T_{max}, $AUC_{0-\tau}$
Secondary	
● To investigate the safety and tolerability of coadministration of ensitrelvir and the COC in healthy adult female participants.	● AE, physical examination, laboratory tests (hematology, blood chemistry, coagulation and urinalysis), vital signs (systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature), and 12-lead ECG
● To investigate the PK of multiple doses of ensitrelvir when coadministered with the COC in healthy adult female participants.	● The following ensitrelvir PK parameters were calculated: C_{max}, T_{max}, $AUC_{0-\tau}$

AE = adverse event; $AUC_{0-\tau}$ = area under the plasma concentration-time curve over the dosing interval τ; COC = combined oral contraceptive; C_{max} = maximum plasma concentration; DRSP = drospirenone; ECG = electrocardiography; EE = ethinyl estradiol; PK = pharmacokinetic(s); T_{max} = time to maximum plasma concentration

Methodology: This was a single-arm, open-label, drug-drug interaction study in healthy adult premenopausal female participants to evaluate the potential effects of ensitrelvir on the pharmacokinetics (PK) of a combined oral contraceptive (COC). The study consisted of a screening period (days −28 to −1), a treatment period (days 1 to 25), and a follow-up period (days 26 to 32 [+2]).

Screening Period

Participants underwent screening evaluations to determine eligibility within 28 days before study intervention administration.

Treatment Period

Participants were admitted to the study site on day −1 for screening until day 1. Participants received a COC (ethinyl estradiol [EE] 0.02 mg and drospirenone [DRSP] 3 mg) once daily from days 1 to 24 (in the fasted state on days 18 to 24) in the morning. Participants visited the study site on day 10 (± 1) for a follow-up. Participants were admitted to the study site on day 18 until discharge on day 25. Participants received ensitrelvir (375 mg on day 20 and 125 mg on days 21 to 24) as coadministration with the COC in the fasted state.

Follow-up Period

Participants came back to the study site for a follow-up visit on day 32 (+2).

Number of Participants (Planned and Analyzed):

Planned: 24

Enrolled: 24

Analyzed for PK:

- PK Concentration Set: 23
- PK Parameter Set: 23

Analyzed for safety:

- Safety Analysis Set: 24

Main Criteria for Inclusion and Exclusion:

1. Inclusion criteria

- Participants had to be ≥ 18 to ≤ 35 years of age at the time of signing the informed consent.
- Body mass index (BMI) within the range of ≥ 18.5 to ≤ 30.0 kg/m^2 at the screening visit.
- Female
  - A female participant was eligible to participate if she was not pregnant or breastfeeding, and either of the following conditions applied:
  - Was a woman of childbearing potential (WOCBP), had not received any oral contraceptives for at least 28 days prior to the first dose of study intervention, and used a highly effective contraceptive method.

2. Exclusion criteria

- History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematologic, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
- History of venous and arterial thrombosis (ie, deep venous thrombosis, pulmonary embolism) or hereditary clotting disorders (in first degree immediate relatives), or participants who were considered to be at high risk of developing thrombosis by the investigator.
- Presence (suspected) or history of having breast cancer, endometrial cancer, or cervical cancer.
- Presence of unexplained genital bleeding.
- Participants who had taken injectable or implantable contraceptives, hormonal intrauterine devices, intrauterine hormone-releasing system within 12 months prior to the first dose of study intervention or hormonal contraceptives (intravaginal or transdermal) for 3 months prior to the first dose of study intervention.

Test Product, Dose and Mode of Administration, Lot Number:

1. Test Product

Intervention Label	**Ensitrelvir**	**COC**
Intervention Name	Ensitrelvir	EE + DRSP
Intervention Description	Tablets	Tablets
Type	Drug	Drug
Dosage Form [of Administration]	Tablets	Tablets
Unit Dose Strengths	125 mg	EE 0.02 mg DRSP 3 mg
Dosage Levels	Day 20: 375 mg Days 21 to 24: 125 mg once daily	Days 1 to 24: EE 0.02 mg + DRSP 3 mg once daily
Route of Administration	Oral	Oral
Use	Experimental	Concomitant
IMP and NIMP	IMP	NIMP
Sourcing	Provided by the sponsor	Provided locally by the site
Packaging and Labeling	Ensitrelvir was provided in blister. Each blister was labeled as required per country requirement	COC was sourced locally
Current/ Former Name or Alias	Not applicable	Not applicable

COC = combined oral contraceptive; DRSP = drospirenone; EE = ethinyl estradiol; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product

2. Dose and Mode of Administration

The study interventions were administrated as shown in the table above.

3. Packaging Lot Number

Ensitrelvir: [redacted]

COC (EE + DRSP): [redacted]

Duration of Treatment:

Ensitrelvir: 5 days

COC: 24 days

Reference Therapy, Dose and Mode of Administration, Lot Number:

Not applicable

Statistical Methods:

Pharmacokinetics Analyses:

Maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and area under the plasma concentration-time curve over the dosing interval τ ($AUC_{0-\tau}$) were calculated for each participant based on the plasma concentration data with the noncompartmental analyses. Calculations were based on the actual sampling times.

The estimated PK parameters were summarized by treatment, day, and nominal sampling time with N (number of analysis set), arithmetic mean (Mean), SD, coefficient of variation (CV%), Geometric Mean, Geometric CV%, Median, minimum (Min), maximum (Max) values. The T_{max} was summarized by treatment with N, Mean, SD, CV%, Median, Min, Max values. If the number of PK parameter data was less than 3, the data were not summarized.

The effect of coadministration of ensitrelvir on the PK of COC (EE and DRSP separately) in the PK Parameter Set was assessed. An analysis of variance (ANOVA) was performed using SAS Proc Mixed for natural log (ln)-transformed C_{max} and $AUC_{0-\tau}$ of EE/DRSP. In case of unbalanced data, the Kenward-Roger method was used to compute the denominator degrees of freedom for the tests of a fixed effect in the analysis. The point estimates and their 90% CIs were generated for the differences between COC coadministered with ensitrelvir and COC administered alone for ln-transformed C_{max} and $AUC_{0-\tau}$. The point estimates and their 90% CIs were back-transformed to obtain the corresponding geometric least squares mean ratios and 90% CIs.

A (EE coadministered with ensitrelvir) vs. B (EE administered alone)

C (DRSP coadministered with ensitrelvir) vs. D (DRSP administered alone)

If the 90% CIs for C_{max} and $AUC_{0-\tau}$ of EE (A/B) and DRSP (C/D) were completely contained within the range of 0.8000 to 1.2500, respectively, then the conclusion would be that ensitrelvir does not significantly affect the PK of COC.

Safety Analyses:

For all safety analyses, the Safety Analysis Set was used. Summary statistics were provided by visit/time for safety endpoints. List of clinically significant abnormal values were presented. Adverse events (AEs) were tabulated and summarized according to the version 27.1 of Medical Dictionary for Regulatory Activities (MedDRA).

All AEs were coded using the MedDRA coding system using System Organ Class (SOC) and Preferred Term (PT). A treatment-emergent adverse event (TEAE) was defined as an AE that begins or increases in severity at or after the first dose of the study intervention. Tabulations for all TEAEs, severity, outcome, causality, AEs leading to discontinuation of study intervention, AEs leading to study discontinuation, and serious adverse events (SAEs) were provided. Tabulations for all TEAEs were provided by stage and overall. A by-participant AE data listing was also provided.

Summary of Results:

Demographics:

All 24 participants were female. A total of 17 participants were White, 6 participants were Black or African American, and remaining 1 participant was Other. The median (min, max) age was 29.5 (19, 35) years, and the mean (SD) BMI was 25.01 (2.568).

Pharmacokinetics:

The geometric mean ratios (90% CIs) (coadministered with ensitrelvir for 1 day [day 20]/alone [day 19]) of $AUC_{0-\tau}$ and C_{max} of EE were 1.0198 (0.9914, 1.0490) and 1.0729 (1.0078, 1.1422), respectively. The geometric mean ratios (90% CIs) (coadministered with ensitrelvir for 5 days [day 24]/alone [day 19]) of $AUC_{0-\tau}$ and C_{max} of EE were 1.0740 (0.9793, 1.1780) and 1.1235 (1.0402, 1.2135), respectively. The geometric mean ratios of $AUC_{0-\tau}$ and C_{max} in both comparisons were close to 1 and their 90% CIs were within the range of 0.8000 to 1.2500.

The geometric mean ratios (90% CIs) (coadministered with ensitrelvir for 1 day [day 20]/alone [day 19]) of $AUC_{0-\tau}$ and C_{max} of DRSP were 1.1032 (1.0718, 1.1356) and 1.0109 (0.9308, 1.0978), respectively. The geometric mean ratios (90% CIs) (coadministered with ensitrelvir for 5 days [day 24]/alone [day 19]) of $AUC_{0-\tau}$ and C_{max} of DRSP were 1.8047 (1.6855, 1.9323) and 1.4974 (1.3769, 1.6285), respectively. The geometric mean ratios of $AUC_{0-\tau}$ and C_{max} in the comparison between day 19 and day 20 were close to 1 and their 90% CIs were within the range of 0.8000 to 1.2500. However, the geometric mean ratios of $AUC_{0-\tau}$ and C_{max} in the comparison between day 19 and day 24 were over 1 and their 90% CIs were not within the range of 0.8000 to 1.2500.

Safety:

No deaths, serious TEAEs, TEAEs leading to discontinuation of study intervention, or TEAEs leading to study discontinuation were reported. A total of 28 TEAEs were reported in 14 participants (58.3%). Of these, 27 TEAEs were mild in severity, and the remaining one (Epstein-Barr virus infection) was moderate in severity and not related to the study intervention. A total of 8 TEAEs reported in 7 participants (29.2%) were ensitrelvir-related and 8 TEAEs reported in 4 participants (16.7%) were COC-related.

All TEAEs were resolved except for 1 TEAE of catheter site erythema, which was mild in severity, not related to either study intervention and resolved with sequelae. No apparent trends were shown in the laboratory parameters, vital sign measurements, 12-lead ECG, or physical examinations after the study intervention administration.

CONCLUSIONS

Ensitrelvir increased DRSP exposure by approximately 1.80-fold when coadministered with ensitrelvir for 5 days. In a drug-drug interaction study of ketoconazole, although DRSP 3 mg exposure increased by 2.7-fold with ketoconazole, it was concluded that this change is not clinically relevant, given that DRSP was well-tolerated even at a 3-fold dose (DRSP 10 mg). In addition to this, given that ensitrelvir has a short treatment duration of 5 days, the increase in exposure of DRSP caused by ensitrelvir can be considered not clinically meaningful.

In conclusion, ensitrelvir 375/125 mg had no clinically meaningful effect on the PK of COC, and was safe and well-tolerated.

Date of Report: 21 May 2025